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# RESULTS OF THE PERFORMANCE VERIFICATION OF THE LABPAD® INR SYSTEM


## Summary

**Aim** Accuracy and measurement repeatability of LabPad® INR device, an innovative point-of-care platform used with Tsmart® INR to monitor warfarin therapy, was evaluated.

**Methods** Study was performed in Grenoble University Hospital using capillary blood from 200 subjects on two Tsmart® INR lots and two LabPad® analysers. Laboratory testing was performed using corresponding venous blood with the core-lab STA-R Evolution® analyzer using CI Plus reagent from Diagnostica Stago. INR results were compared according to the ISO 17593:2007 standard.

**Results** INR results showed strong correlation with core-lab system. All acceptance criteria based on ISO standards guidelines for accuracy were met.


## Introduction

Long-term use of oral anticoagulant treatment using Vitamin K Antagonists (VKA) is commonly used to prevent thromboembolic events[1]. Optimal dosage is difficult to achieve because of variable dose-response between individuals and interactions with drugs and food. Bleeding is thus a serious and potentially fatal complication of VKA. A regular testing of coagulation time, known as PT/INR test (prothrombin time/International Normalized Ratio), is thus mandatory to maintain the optimal therapeutic range. In this context, several studies have demonstrated the high value of POC instruments for monitoring patients under VKA therapy[2,3,4.]

The device, LabPad® INR, measures blood coagulation time thanks to a patented optical technology. This portable In-Vitro Diagnostics (IVD) device works with the Tsmart® INR, a microcuvette containing a procoagulant reagent embedded in dried form. It can easily and quickly perform accurate INR tests from a small drop of capillary blood.

In this study, the analytical performance of the LabPad® INR system were evaluated.

## Methods

### *General*

A total of 200 subjects comprising 20 normal donors and 180 patients receiving vitamin K antagonists (VKAs) therapy were enrolled in the study at the Clinical Investigation Center (Grenoble University Hospital). All provided a written consent to participate.

The study was conducted using two different lots of Tsmarts®, and two different LabPad®. Each lot of Tsmart® had been previously calibrated according to the World Health Organization guidelines using International Reference Preparation and tilt tube method[5].

Subjects provided four consecutive separate finger-stick blood samples from the same hand. Skin punctures were performed on the pad of index and middle fingers for testing the first lot and of ring and little finger for testing the second lot as described in table 1. Puncture were performed by three different healthcare professionals. To apply the drop on the POC system, the finger of patient was gently and carefully approached by the nurse toward the microcuvette Tsmart® INR, with no need of an extra collection device.

| Drops | Fingers | Conditions | |
|---|---|---|---|
| Drop 1 | Index | 1st measurement | LOT 1 LabPad 1 |
| Drop 2 | Middle | 2nd measurement | |
| Drop 3 | Ring | 1st measurement | LOT 2 LabPad 2 |
| Drop 4 | Little | 2nd measurement | |

*Table 1: Proceedings of the clinical study: capillary blood sample*

Venous blood were obtained from the same subjects within few minutes of taking the capillary sample, for preparation of citrated plasma and testing in duplicate according to the routine laboratory method using the STA-R Evolution® system and Neoplastine® CI PLUS reagent from Diagnostica Stago. INR returned by this core-Lab system was previously compared to the reference INR obtained by the "tilt-tube" method using international reference preparation supplied directly from the National Institute for Biological Standards and Control. Correlation between laboratory method and universal method was shown to be excellent with a slope of 0.99 (95% IC 0.95 to 1.03) with an intercept of 0.02 (95% IC -0.05 to 0.08), thus validating the laboratory method using the STA-R Evolution® system and Diagnostica Stago Neoplastine® CI PLUS reagent as a secondary reference for evaluating the performance of the LabPad® INR portable device.

***Methods comparison***
Data were first analyzed to highlight potential outliers. Trueness and accuracy were then evaluated by performing method comparison according to the criteria fixed in the ISO standard 17593:2007[6]. Statistical analysis was performed using STAT-A software. Regression analysis was performed after the method of Passing-Bablock[7], which gives an assessment of agreement of methods. The slope and intercept of the regression plot and their 95% confidence interval (CI) were calculated. The quality of data was assessed by evaluating the correlation coefficient. Deviation from the linearity was checked using the Cusum test.

***Repeatability***
Each subject underwent two finger-sticks in order to perform dual measurements within a short period of time for each lot. Comparison of duplicate measurement results is used to assess repeatability.
The analysis procedure used is described in the ISO standard 17593:2007 (paragraph 8.4.4.1). Prior to analysis, a "Duplicate Range Limit" (DRL) was calculated for each patient, and the range between the two measurements was compared to this limit. Range exceeding the acceptable difference between duplicates indicated sample instability which have to be excluded from analysis.
The average (arithmetic mean of all measurements), standard deviation (SD) and its upper confidence limit were calculated as well as the coefficient of variation (CV). Calculations were done for each of the following INR ranges: healthy donor, <2.00, 2.00 to 3.00, 3.00 to 4.50, and >4.50, as described in the ISO standard 17593:2007 (paragraph 8.4.4.2).

**Results**
***General***
The distribution of INR values showed mostly normal or low INR values (table 2).

| INR range | Subjects number |
|---|---|
| Below 2.0 | 67 |
| From 2.0 to 3.0 | 100 |
| From 3.0 to 4.5 | 33 |
| Above 4.5 | 0 |

*Table 2: distribution of INR values*

***Method comparison***
Results of the data set were plotted and analyzed along the ISO17593:2007 guidelines including linear regression, Bland-Altman plot, accuracy and bias calculation.
Mean results from both drops of finger stick blood from subjects were used to determine the closeness of agreement between the results and the reference value.
Strong correlation of LabPad® system with the STA-R-Neoplastine® CI PLUS system reference was shown as illustrated in figure 1.

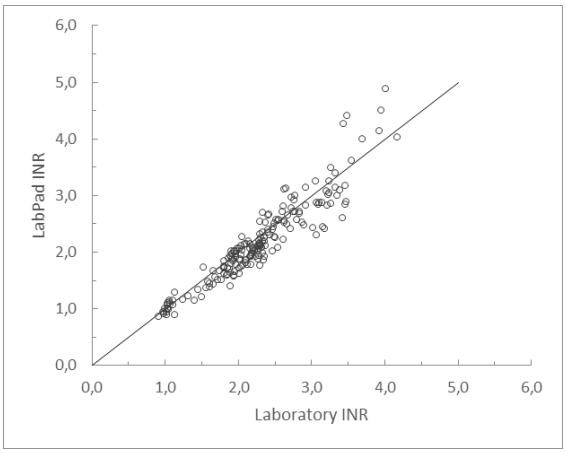


*Figure 1: LabPad® system INR results (Lot 1) vs STA-R-Neoplastine® CI PLUS system INR results*

Passing-Bablock regression yielded a slope of 1.01 (95% IC 0.97 to 1.06) with an intercept of -0.13 (95% IC -0.24 to -0.04) for the first lot and a slope of 0.94 (95% IC 0.90 to 1.00) with an intercept of 0.04 (95% IC -0.08 to 0.13) for the second lot. Moreover, correlation coefficients were respectively 0.965 and 0.950, indicating that the LabPad® values for both lots were closely correlated to the reference values within therapeutic range up to 4.5.

Moreover, the Bland-Altman plot (figure 2) showed a mean absolute difference (average bias) of -0.1 with 95% limits of agreements between -0.52 and 0.32 (1.96 SD). The low bias was nevertheless found to be in the ISO acceptable limits of +/- 0.3 INR.

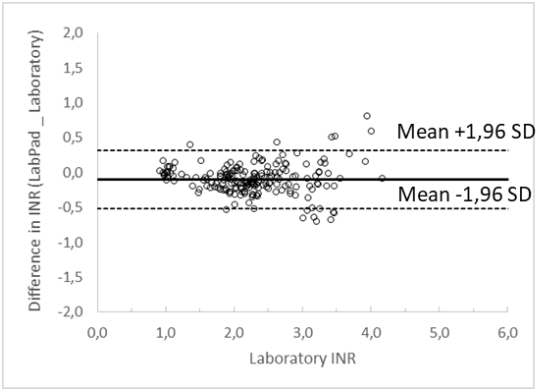


*Figure 2: Bland-Altman plot showing differences between LBP® INR results (Lot 1) and INR Laboratory reference results and bias. Dashed line are equivalent to mean bias +/- 1.96 SD.*

Parameters obtained for lot 2 were similar as shown by table 3.

| | Bland Altman parameters | Estimate | 95% CI lower bound | 95% CI upper bound |
|---|---|---|---|---|
| LOT 1 | Bias | -0,10 | -0,52 | 0,32 |
| | SD | 0,21 | | |
| LOT 2 | Bias | -0,08 | -0,56 | 0,39 |
| | SD | 0,24 | | |

*Table 3: Results for bias, standard and standard deviation for lots 1 and 2.*

Trueness was then assessed by expressing the percentage of differences between the LabPad® INR results and the STA-R-Neoplastine® CI PLUS system values within defined limits (table 4). Minimum acceptable trueness according to ISO 17593:2007 requires that more than 90% of the differences to the reference shall fall within the limits of ± 0.5 INR for INR below 2.0 and ± 30% for INR between 2.0 and 4.5.

| INR interval | Allowable difference (90% of results) | Results between allowable difference | |
|---|---|---|---|
| Below 2.0 | ± 0,5 | LOT 1 | 98,50% |
| | | LOT 2 | 100% |
| From 2.0 to 4.5 | ± 30% | LOT 1 | 100% |
| | | LOT 2 | 100% |

*Table 4: Assessment of the trueness of LabPad® INR results versus STA®-Neoplastine® CI PLUS system according to ISO requirements. .*

Table 4 shows that LabPad® INR is fully complying with the requirements of the ISO 17593:2007 guidelines as more than 98% of all INR differences were found within the acceptable limits. Moreover, analysis was done for limits within ± 0.3 for INR below 2.0 and ± 20% for INR between 2.0 and 4.5 as suggested by ISO 17593:2007 without any requirements (table 5).

| INR interval | Within | LOT 1 | LOT 2 |
|---|---|---|---|
| Below 2.0 | ± 0,3 | 95,5 | 97,0% |
| From 2.0 to 4.5 | ± 20% | 95,4 | 93,2% |

*Table 5: Assessment of the trueness of LabPad® INR results versus STA®-Neoplastine® CI PLUS system*

Table 5 shows that even when applying the more stringent limits, as recommended by CLSI guidelines[8], more than 90% of the differences are within these limits.

***Precision***

The mean prothrombin time, standard deviation (SD), its upper confidence limit and coefficient of variation (CV) are calculated for each interval for both lots (table 6).

| **LOT 1** | Healthy donors | below 2 | 2.0 to 3.0 | 3.0 to 4.5 | All range |
|---|---|---|---|---|---|
| Mean | 1.03 | 1.66 | 2.26 | 3.28 | 2.17 |
| SD | 0.046 | 0.092 | 0.122 | 0.243 | 0.140 |
| Higher 95% IC of SD | 0.046 | 0.117 | 0.143 | 0.325 | 0.156 |
| **CV** | **4.5%** | **5.5%** | **5.4%** | **7.4%** | **6.5%** |
| | | | | | |
| **LOT 2** | Healthy donors | below 2 | 2.0 to 3.0 | 3.0 to 4.5 | All range |
| Mean | 1,13 | 1,71 | 2,25 | 3,16 | 2,14 |
| SD | 0,072 | 0,101 | 0,145 | 0,205 | 0,141 |
| Higher 95% IC of SD | 0,108 | 0,129 | 0,17 | 0,283 | 0,158 |
| **CV** | **6,4%** | **5,9%** | **6,4%** | **6,5%** | **6,6%** |

*Table 6: Precision parameters for lots 1 and 2.*

Acceptable results were obtained for both lots with overall CV of 6.5% and 6.6% respectively.

**Conclusion**

Strong correlation of LabPad® with the STA-R Evolution® system using Neoplastine® CI PLUS reagent was shown: A linear regression yielded a slope close to 1 and an intercept inferior to 0.15 for both lots. The accuracy proved to be excellent with more than 90% of all INR differences for both lots within the acceptable limits according to ISO 17593:2007 or CLSI guidelines (POCT14).
The system proved to be reliable and robust as shown by the analysis of precision giving a CV around 6.5%.

All these results showed that trained healthcare professionals can use the LabPad® INR to monitor patients on VKA drugs in full confidence.

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